

## COMPARISON OF SIDE EFFECTS OF MISOPROSTOL BY ORAL AND RECTAL ROUTES IN ACTIVE MANAGEMENT OF THIRD STAGE OF LABOUR

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### ABSTRACT

#### BACKGROUND

Every year, there are 14 million cases of PPH. It accounts for about 25% of maternal deaths worldwide. This can be reduced by active management of third stage of labour. Administration of misoprostol after delivery of neonate has been shown to be effective in reducing amount of blood loss during delivery.

The aim of the study is to compare the side effects of misoprostol in terms of distribution, frequency and severity by oral and rectal route for active management of third stage of labour.

#### MATERIALS AND METHODS

A prospective randomised study conducted on 100 women in labour in Department of OBG in MVJMC and RH. They were divided into 2 groups of 50 parturient mothers each group receiving misoprostol (600 µg) by oral route (Group 1) and rectal route (Group 2). Outcome of these women were noted in terms of blood loss, duration of 3<sup>rd</sup> stage of labour and side effects like shivering, fever, diarrhoea, nausea and vomiting.

#### RESULTS

There was not much difference in amount of blood loss and duration of third stage among the two groups. However, side effects were more in the group receiving misoprostol orally (32%) as compared to that receiving by rectal route (14%).

#### CONCLUSION

In the present study, both oral and rectal routes are effective in active management of third stage of labour. However, rectal route has lesser side effects.

#### KEYWORDS

Misoprostol, Active Management of Third Stage of Labour, Adverse Effects, Postpartum Haemorrhage.

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#### BACKGROUND

Third stage of labour refers to the period following the complete delivery of newborn until the complete delivery of placenta. All women who deliver are at risk of complications in the third stage of labour. These complications include PPH, retained placenta and uterine inversion. Others include conditions that commonly manifest for the first time during the third stage of labour.

#### Management of Third Stage of Labour

The chief objectives during the management of third stage of labour are as follows-

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1. Natural separation of the placenta and the membranes and their complete expulsion should be promoted.
2. Blood loss to be minimised.
3. Good and permanent contraction and retraction of the uterus have to be secured.

#### Active Management of Third Stage (AMTSL)<sup>1,2,3</sup>

The underlying principle in active management is to excite powerful uterine contractions following birth of baby by parenteral oxytocics, which facilitates not only separation of placenta, but also produces effective contractions following separation.

AMTSL has been defined in various ways and current international definition comprises three components.<sup>4,5</sup>

Active management conventionally includes the following-

1. Uterotonic drugs should be administered after the delivery of foetus.
2. Controlled cord traction of umbilical cord to be done for placental delivery.

3. Uterus should be massaged following delivery of placenta followed by the palpation of the uterus every 15 minutes for 2 hours to assess the continued need for massage.

Misoprostol is synthetic 15-deoxy-16-hydroxy-16-methyl analogue of prostaglandin E1 is another drug with strong uterotonic property. It has numerous advantages as it can be administered through various routes like orally, rectally, sublingually or vaginal route. It is easy to store and stable at room temperature. Many studies have established the efficacy of the prophylactic use of misoprostol for reduction of blood loss after delivery when compared to conventional syntocinon<sup>3,6-8</sup> or methylergometrine.

Although, misoprostol can be used by different routes, still the most effective route with fewer side effects has yet to be established. So, this comparative study is being undertaken to know the efficacy and side effects of misoprostol administered by oral, sublingual and rectal routes in the management of third stage of labour.

Misoprostol tablet contains hydroxypropyl methylcellulose, microcrystalline cellulose, sodium starch glycolate and hydrogenated castor oil.

### Metabolism<sup>9</sup>

Misoprostol is rapidly metabolised in lungs, brain, liver and other tissues. It is converted to 15-keto derivatives by the activity of enzyme 15-hydroxy PG dehydrogenase. These are converted to 13, 14 dihydro 15-keto compounds that undergo beta oxidation and alpha oxidation to be transformed into a wide variety of products that are excreted in urine and faeces.

### Oral Route<sup>10</sup>

After oral administration, misoprostol is rapidly and almost completely absorbed from gastrointestinal tract. Then, the drug undergoes extensive and rapid first pass metabolism by de-esterification to form misoprostol acid. Following a single dose of 400 µg oral drug, the plasma levels increase rapidly and peaks at about 30 minutes and declines rapidly by 120 minutes and remains low thereafter. The onset of action of misoprostol is 8 mins. by oral route while it's duration of action is 2 hours.

### Rectal Route<sup>11</sup>

The rectal route of administration has been studied recently for the management of PPH. This route is less commonly used for other applications. The onset of action of misoprostol is 10 mins. by rectal route while it's duration of action is 4 hours.

Adverse effects of misoprostol includes<sup>12,13,14</sup> abdominal pain, nausea, vomiting, diarrhoea, constipation, dyspepsia, flatulence, headache, lethargy, fever, chills, teratogenicity, tonic uterine contractions, foetal bradycardia, uterine rupture, uterine pain and pelvic pain.

## AIMS AND OBJECTIVES

To compare the side effects of misoprostol in terms of distribution, frequency and severity by oral and rectal route for active management of third stage of labour.

## MATERIALS AND METHODS

100 antenatal women admitted to labour room undergoing normal vaginal delivery at MVJ Medical College and Research Hospital were enrolled in the study as per formulated inclusion and exclusion criteria after counseling and taking informed written consent. Gestational age of all patients was calculated their Last Menstrual Period (LMP), early ultrasonography (dating scan)/clinical examination details. A thorough clinical history and examination was done.

100 patients were divided into 2 groups of 50 in each.

After delivery of baby (within 1 minute of cord clamping and cutting), Group 1 (50) patients were given oral misoprostol (600 mcg) and Group 2 (50) patients received rectal misoprostol (600 mcg).

In both the groups, duration of third stage of labour, amount of blood loss and side effects were noted and results were recorded and analysed. The amount of blood loss was measured by collecting blood using a drape and measuring it using a measuring jar. The preweighed gauze pieces was used and difference in weight in grams gave the amount of blood loss in mL (1 mL of blood weighs approximately 1 g).

Haemoglobin and haematocrit estimation was done after 48 hours of delivery.

### Inclusion Criteria

- Singleton pregnancy.
- Cephalic presentation.
- Normal vaginal delivery either spontaneous or induced.
- Gestational age 37-42 weeks.
- Gravida <4.

### Exclusion Criteria

- Hypersensitivity to prostaglandins.
- Previously scarred uterus.
- Patients with medical and obstetrics complications.
- Haemoglobin <8 gm%.
- Malpresentations.
- Multiple pregnancies.
- Traumatic PPH.
- Grand multipara.

## RESULTS

Age in Years	Group1 (Oral)	Group2 (Rectal)	Total
<20	5 (10%)	0 (0%)	5 (5%)
20-30	42 (84%)	46 (92%)	88 (88%)
31-40	3 (6%)	4 (8%)	7 (7%)
<b>Total</b>	<b>50 (100%)</b>	<b>50 (100%)</b>	<b>100 (100%)</b>
<b>Mean±SD</b>	<b>24.07±3.67</b>	<b>24.17±2.94</b>	

**Table 1. Age Distribution of Two Groups of Patients Studied**

P value- 0.069 Not significant chi-square- 5.32

The mean age in Group 1 (oral) is  $24.07 \pm 3.67$ . The mean age in Group 2 (rectal) is  $24.17 \pm 2.94$ . Patients in both groups were equally distributed. Maximum numbers of patients are between 20-30 years- 88%, of which 84% were in Group 1 (oral) and 92% in Group 2 (rectal).

Parity	Group 1 (Oral)	Group 2 (Rectal)	Total
Primi	23 (46%)	24 (48%)	47 (47%)
Multi	27 (54%)	26 (52%)	53 (53%)
<b>Total</b>	<b>50 (100%)</b>	<b>50 (100%)</b>	<b>100 (100%)</b>

**Table 2. Parity Distribution in Two Groups of Patients Studied**

**P value- 0.8411, Not significant, chi-square test- 0.0401.**

47% of women in study population were primigravida and 53% were multigravida. 46% of patients in Group 1 (oral) were primigravida and 54% were multigravida. 48% of patients in Group 2 (rectal) were primigravida and 52% were multigravida.

Duration of 3 <sup>rd</sup> Stage (Min.)	Group 1 (Oral)	Group 2 (Rectal)	Total
<8	8 (16%)	4 (8%)	<b>12 (12%)</b>
8-14	42 (84%)	41 (82%)	<b>83 (83%)</b>
>14	0 (0%)	5 (10%)	<b>5 (5%)</b>
<b>Total</b>	<b>50 (100%)</b>	<b>50 (100%)</b>	<b>100 (100%)</b>
<b>Mean Duration of 3<sup>rd</sup> Stage</b>	<b>9.24<math>\pm</math>1.93</b>	<b>10.58<math>\pm</math>2.67</b>	

**Table 3. Duration of 3<sup>rd</sup> Stage (min.) in Two Groups of Patients Studied**

**P value- 0.042, Significant, chi-square test- 6.34.**

12% of patients had third stage duration less than 8 mins., 83% of patients had it between 8-14 mins. and 5% had it more than 14 minutes.

16% of patients in Group 1 (oral) had duration of 3<sup>rd</sup> stage of labour less than 8 minutes, whereas it was 8% in group 2 (rectal). No patient in Group 1 (oral) had duration of third stage more than 14 minutes, whereas 10% patients in Group 2 (rectal) had duration of third stage more than 14 minutes.

Side Effects	Group 1 (Oral)	Group 2 (Rectal)	Total
Nil	34 (68%)	43 (86%)	77 (77%)
Yes	16 (32%)	7 (14%)	23 (23%)
• S	6 (12%)	2 (4%)	8 (8%)
• FE	2 (4%)	3 (6%)	5 (5%)
• DI	4 (8%)	0 (0%)	4 (4%)
• N and V	4 (8%)	2 (4%)	6 (6%)

**Table 4. Side Effects in Two Groups of Patients Studied**

S- Shivering, FE- Fever, DI- Diarrhoea, N and V- Nausea and Vomiting.

P value- 0.032 Significant chi-square- 4.573.

Side effects were seen in 23% of patients, which was more in Group 1 (oral) and was 32%. In Group 2 (rectal), 14% of patients had side effects.

Shivering was the most common effect seen in 8% of patients and least being diarrhoea in 4% of patients. In Group 1 (oral), patients had shivering (12%) as most common side effect, whereas in Group 2 (rectal)- 6%, fever was more common.

Blood Loss (mL)	Group 1 (Oral)	Group 2 (Rectal)	Total
<100	0 (0%)	0 (0%)	<b>0 (0%)</b>
100-200	2 (4%)	0 (0%)	<b>2 (2%)</b>
200-300	16 (32%)	10 (20%)	<b>26 (26%)</b>
300-400	21 (42%)	27 (54%)	<b>48 (48%)</b>
400-500	8 (16%)	5 (10%)	<b>13 (13%)</b>
>500	3 (6%)	8 (16%)	<b>11 (10%)</b>
<b>Total</b>	<b>50 (100%)</b>	<b>50 (100%)</b>	<b>100 (100%)</b>
<b>Mean<math>\pm</math>SD</b>	<b>356<math>\pm</math>102.79</b>	<b>398.20<math>\pm</math>119.2</b>	

**Table 5. Blood Loss (mL) Distribution in Two Groups of Patients Studied**

**P value- 0.131, Not significant, chi-square test- 7.09.**

Mean amount of blood loss in Group 1 (oral) was 356 mL and in Group 2 (rectal) was 398.20 mL. The difference in mean blood loss among two groups were statistically non-significant. P value- Significant, Chi-square test- 16% of patients in Group 2 (rectal) had blood loss of more than 500 mL, whereas in Group 1 (oral) it was 6%.

## DISCUSSION

Misoprostol is the ideal drug with distinct therapeutic advantages, which include stability at high temperatures, cost effectiveness, simple routes of administrations and minimal side effects. The effectiveness of misoprostol in reducing blood loss and preventing PPH has been proven by various studies, but the most effective route has not yet been established. We compared the oral and rectal route of administration of misoprostol for the management of third stage of labour and to note the outcome of these women in terms of blood loss, duration of third stage of labour and side effects like shivering, fever, diarrhoea, nausea and vomiting.

Misoprostol has minimal side effects, which were self-limited like nausea, vomiting, shivering and fever. The incidence was more in oral routes. The reason behind this is highest peak concentration of misoprostol achieved in these routes. In our study, 23% of study population had side effects of which shivering being most common (8%) and diarrhoea being least (4%). The incidence of side effects in Group 1 (oral) was 32% and in Group 2 (rectal), it was 14%. The incidence of shivering (12%) and nausea and vomiting (8%) was highest in Group 1 (oral) compared to rectal group. This correlates with the studies conducted

in 2001<sup>15</sup> and 2006,<sup>16</sup> which concluded the incidence of shivering and pyrexia was significantly higher in group receiving misoprostol by oral route. It also correlates with studies conducted in 2003<sup>11</sup> and 2012,<sup>17</sup> which concluded misoprostol given rectally has lower peak levels and reduction in adverse effects compared with oral route.

The mean blood loss in third stage of labour in Group 1 (oral) was 356±102.79 mL and in Group 2 (rectal) was 398.20±119.2 mL. The maximum blood loss of more than 500 mL was seen in 11 cases of which 8 cases were from Group 2 (rectal), whereas Group 1 (oral) had 3 cases. Mean blood loss was more in Group 2 (rectal) in comparison to Group 1 (oral). In a similar study conducted in 2012,<sup>17</sup> which showed blood loss in group receiving oral misoprostol administration was more in comparison to group with rectal administration. There is no obvious explanation of this discrepancy.

The mean duration of third stage of labour was less than 10 minutes both groups. The mean duration of third stage of labour in Group 1 (oral) was 9.24±1.93 minutes and in Group 2 (rectal) was 10.58±2.67 minutes. In the study conducted in 2012<sup>17</sup> where duration of third stage of labour was more in group receiving misoprostol by oral administration when compared to group receiving rectal administration of misoprostol. There is no obvious explanation of this discrepancy.

## CONCLUSION

Administration of misoprostol (600 mcg) by oral and rectal routes were safe and effective in reducing duration of third stage of labour reducing the amount of blood loss and prevention of PPH. Side effects like shivering, fever, diarrhoea, nausea and vomiting were seen with both routes of misoprostol administration, but they were more common in parturients receiving misoprostol by oral administration.

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